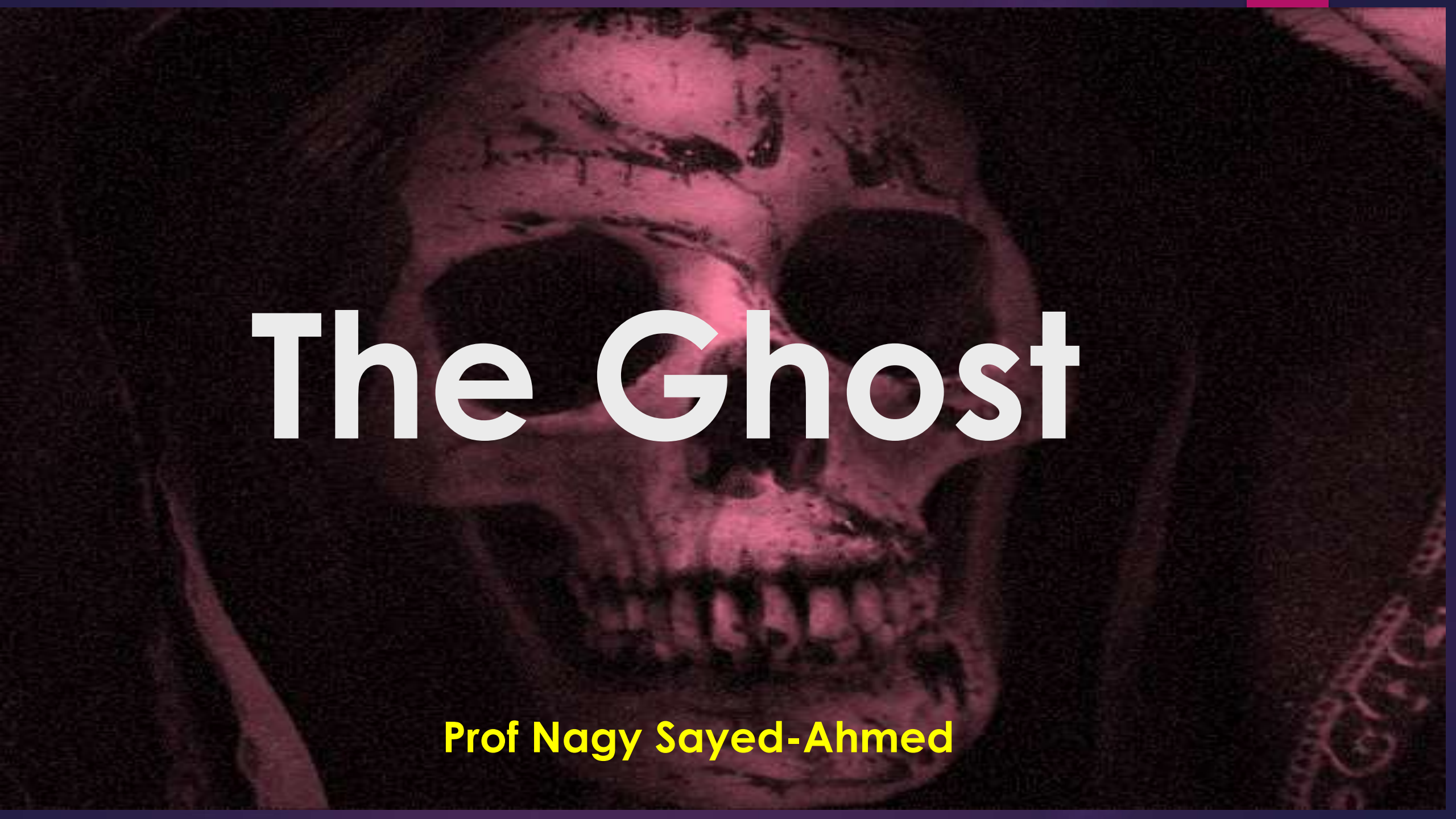


The Ghost

Prof Nagy Sayed-Ahmed

The Ghost

- **Phantom**, **Apparition**, **Spirit**, **Spook**, or **Haunt**
- **The soul or spirit of a dead person or animal that can appear, in visible form or other manifestation, to the living**

The Ghost

- Deceased ancestors: venerable & imagined as having a continued presence in some sort of **afterlife**
- The spirit of a deceased person which remains present in the material world (viz. a ghost) is regarded as an unnatural or **undesirable** state of affairs
- The idea of ghosts is associated with a reaction of **fear**.

Case Scenario 1-1

- 66-yr-old female
- Diabeic for 22 yrs; HTN 5 yrs; G. edema ~1 yr
- On multiple diuretics, anti HTN for 4 months & Insulin "Basal/bolus"
- Presents with progressive weakness 3 weeks, lethargy 5 days & irritability 2 days, vomiting
- Lost 15 kg wt last month

Case Scenario 1-2

- Confused & irritable. Afebrile – no meningism
- BP 90/60, Pulse 110/m regular, RR 22/min
- G. edema but wrinkled skin, JVP increased
- Signs of Rt pleural effusion to midzone
- Shifting dullness & firm rounded bodered hepatomegaly
- Bulbar manifestations

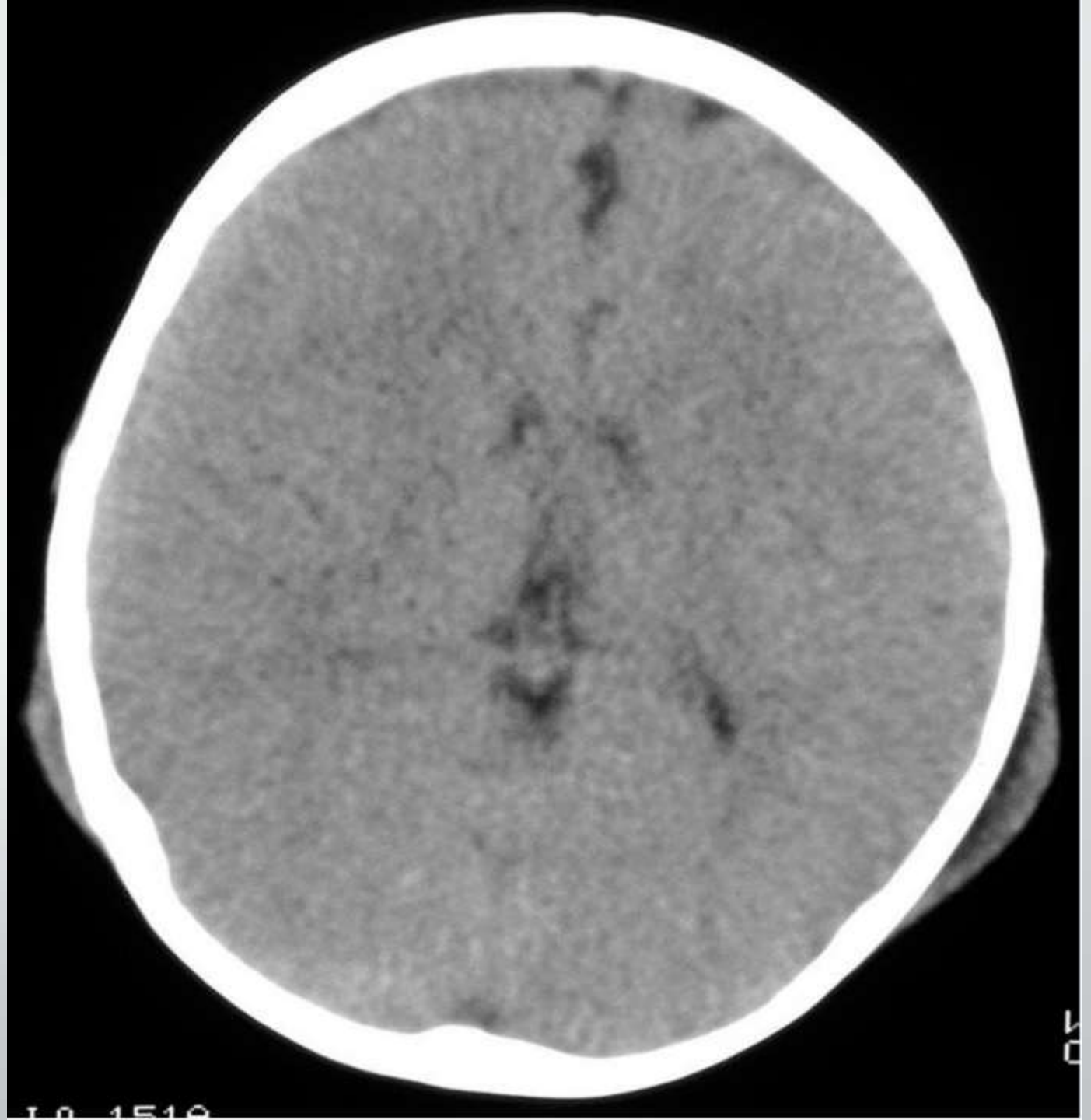
Case Scenario 1-3

- Urine output 20 ml/hour pale yellow (Foley's catheter)
- Proteinuria 3+
- Serum Cr 2.4 mg/dl, BUN 88 mg/dl
- RBG 156 mg/dl, Serum Alb 21 g/L, other LFT normal
- Hb 9.1 g/dl, TLC 7.3, Plt 150 ($X10^3$/cmm)
- SNa 103, SK 1.92, $SHCO_3$ 16, pH 7.31, PO_2 73

Case Scenario 1-4

- ECG: prom U wave, diffuse ST-T changes, frequent PVCs
- CXR: confirms Rt Pleural effeusion
- Abd US: Bright liver, normal PV, normal spleen, normal kidneys, mod. Ascites
- Echocardio. Dilated CM, EF 45%
- Brain CT: ……

Brain CT showing Cerebral Edema



Case Scenario 1-5

- Diagnosis??

- Management???

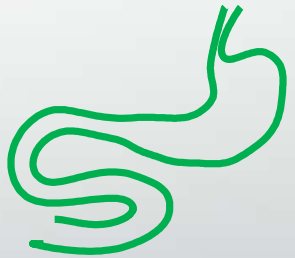
Sings & Symptoms of Hyponatremia

The development and severity of signs & symptoms of hyponatremia depend on:

***Severity *Rate of decline *Age of pt**

Brain requires time to extrude osmoles

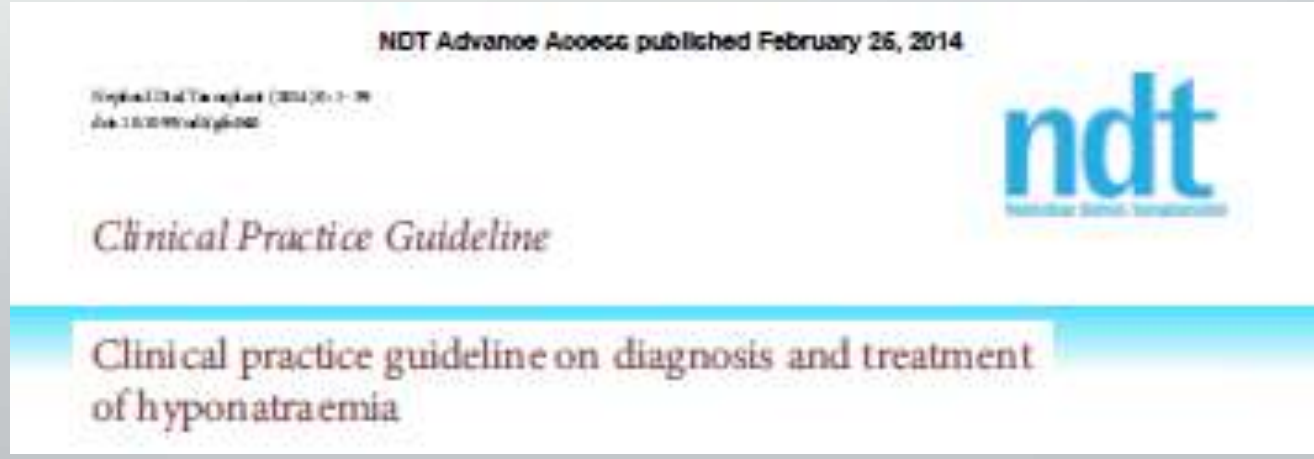
*** muscle cramps * lethargy**
*** disorientation * agitation**
*** ↓ level of conc. * ↓ D.T.reflexes**
*** path. reflexes * C.S. respiration**
*** hypothermia * pseudobulbar palsy**
*** seizures * coma**



Anorexia
Nausea
Vomiting

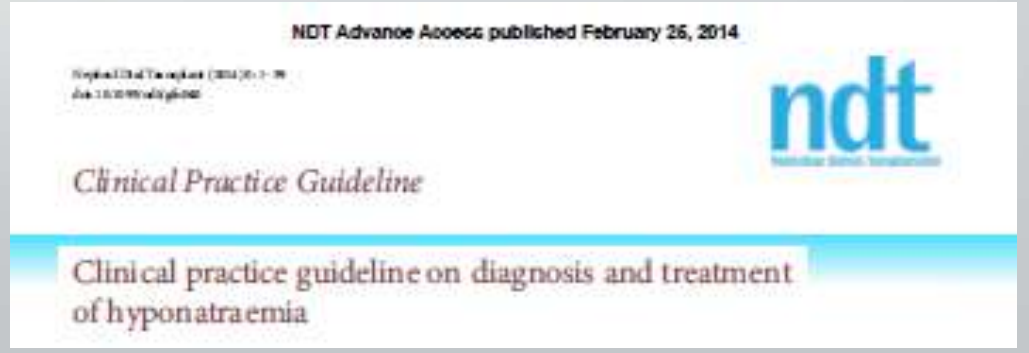
Classification of hyponatremia

- Based on biochemical severity:
  - Mild: 130-135
  - Moderate: 125-129
  - Severe: <125
- Based on time of development: Acute or chronic



Classification of hyponatremia

Severity	Symptom
Moderately severe	Nausea without vomiting
	Confusion
	Headache
Severe	Vomiting
	Cardiorespiratory distress
	Abnormal and deep somnolence
	Seizures
	Coma (Glasgow Coma Scale ≤8)



Hyponatremia

Plasma Osmolality

True Hyponatremia

Hypoosmolar

Hyperosmolar Hyponatremia

Hyperosmolar

Pseudohyponatremia

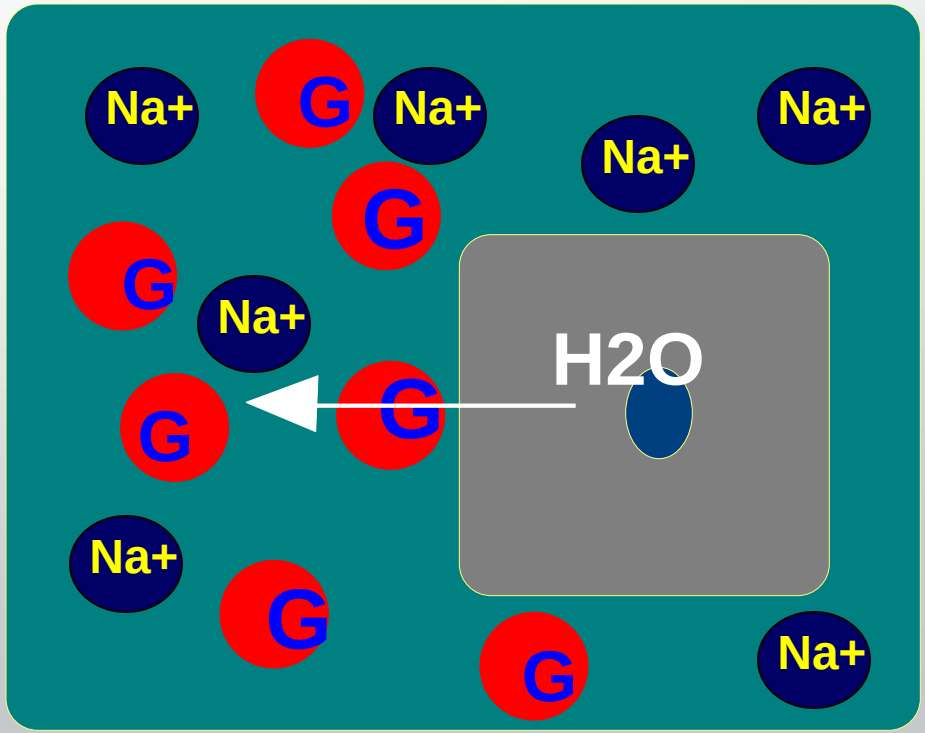
Normosmolar

Hyperosmolar Hyponatremia

Distributional
Osmotic-related

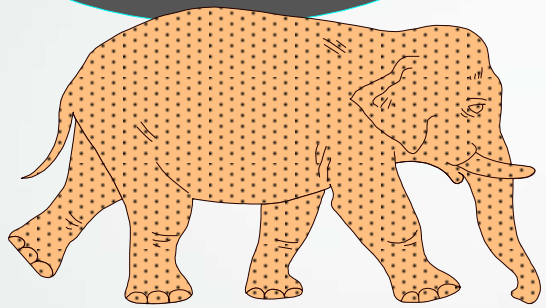
Osmotically-active material in plasma
e.g.
glucose, mannitol, methanol etc...

100 mg/dl ↑ in plasma glucose → 1.6 mmol/L ↓ in plasma Na

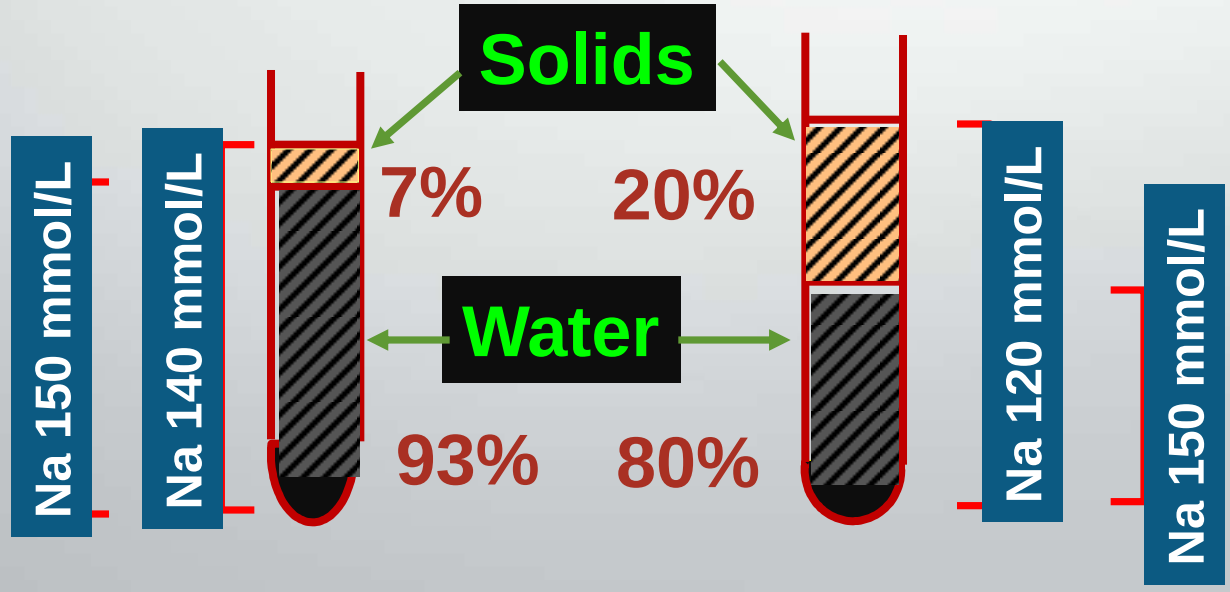


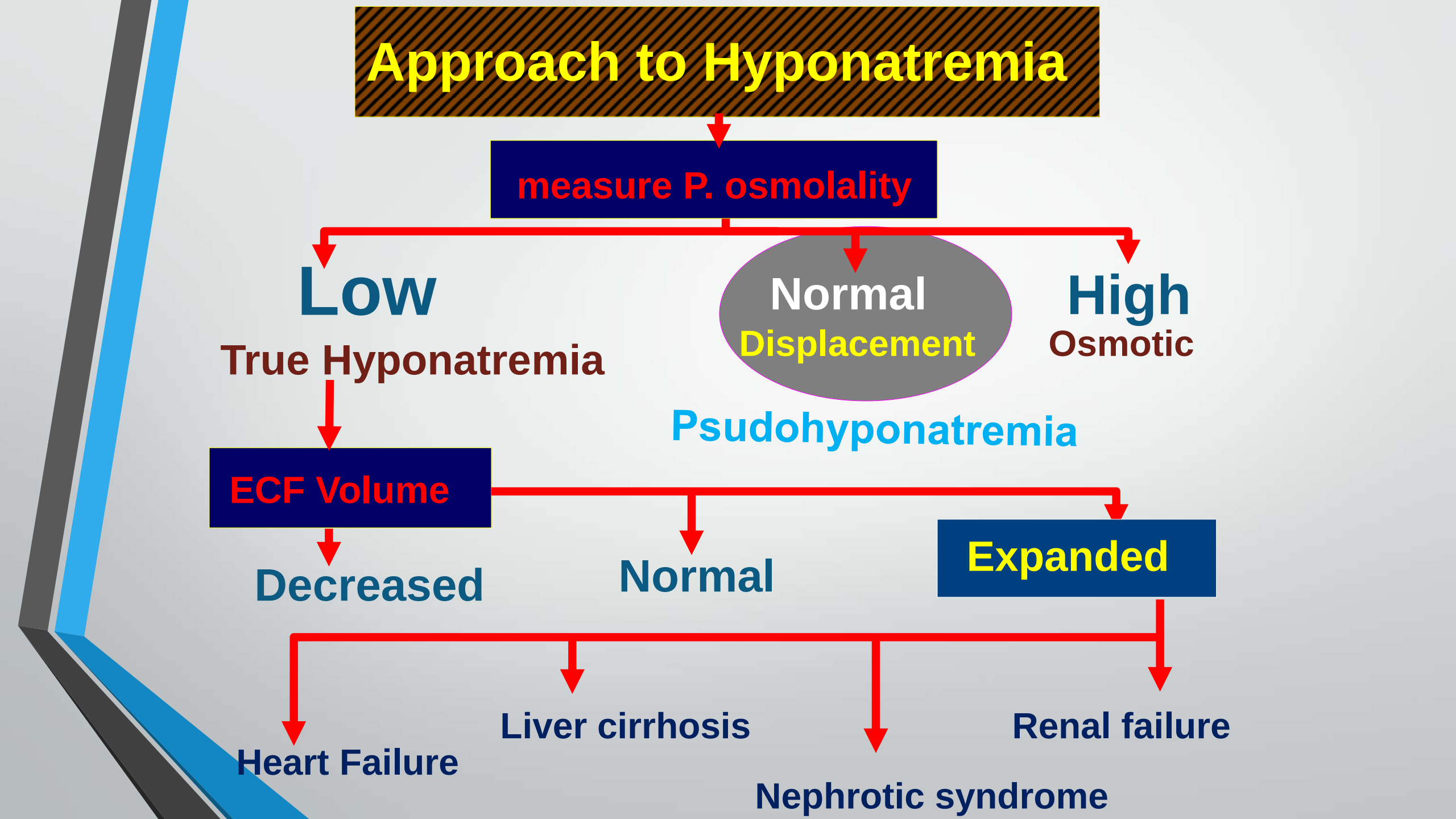
Pseudohyponatremia

Displacement

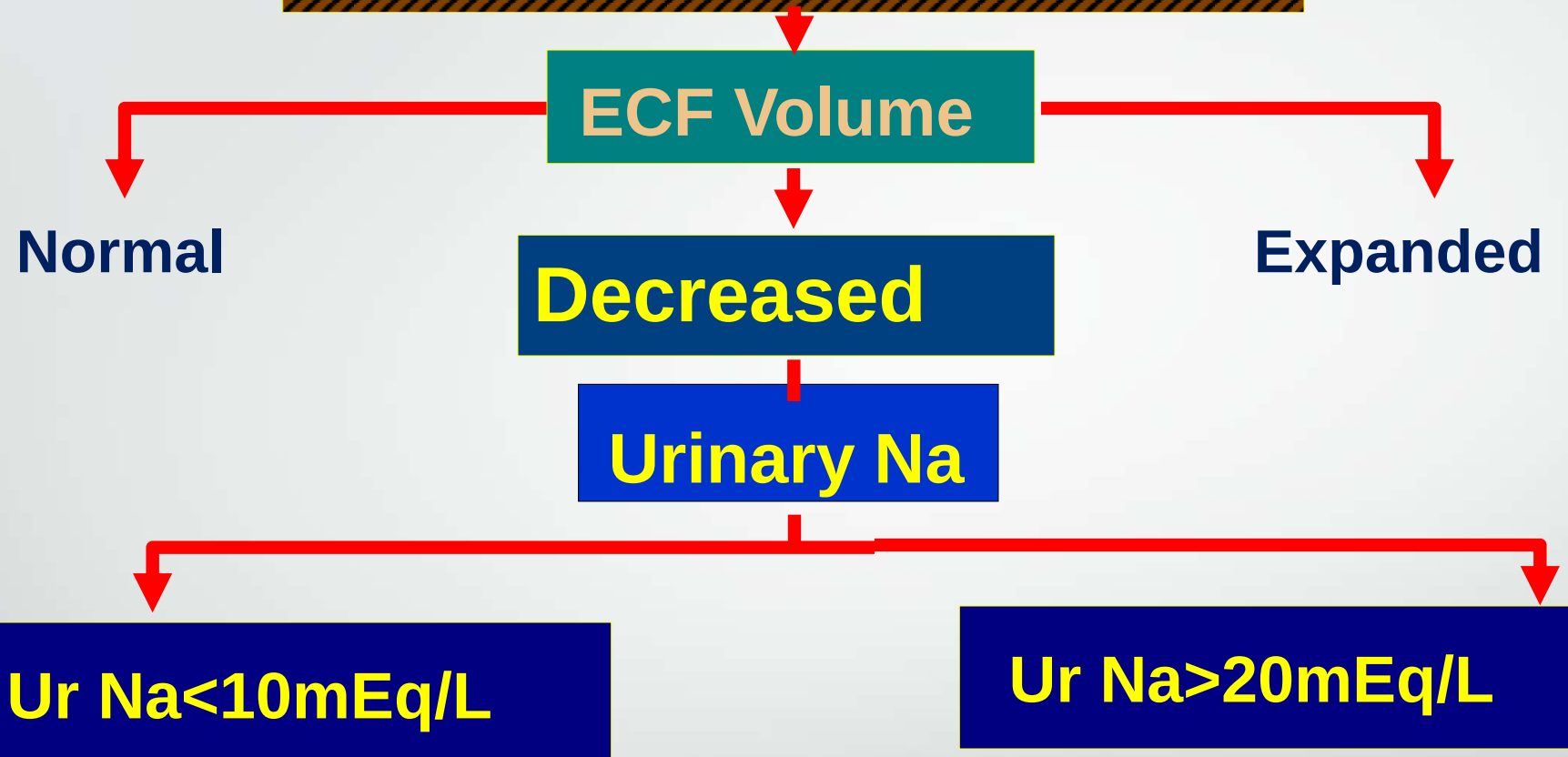


Hyperlipidemia
Hyperproteinemia



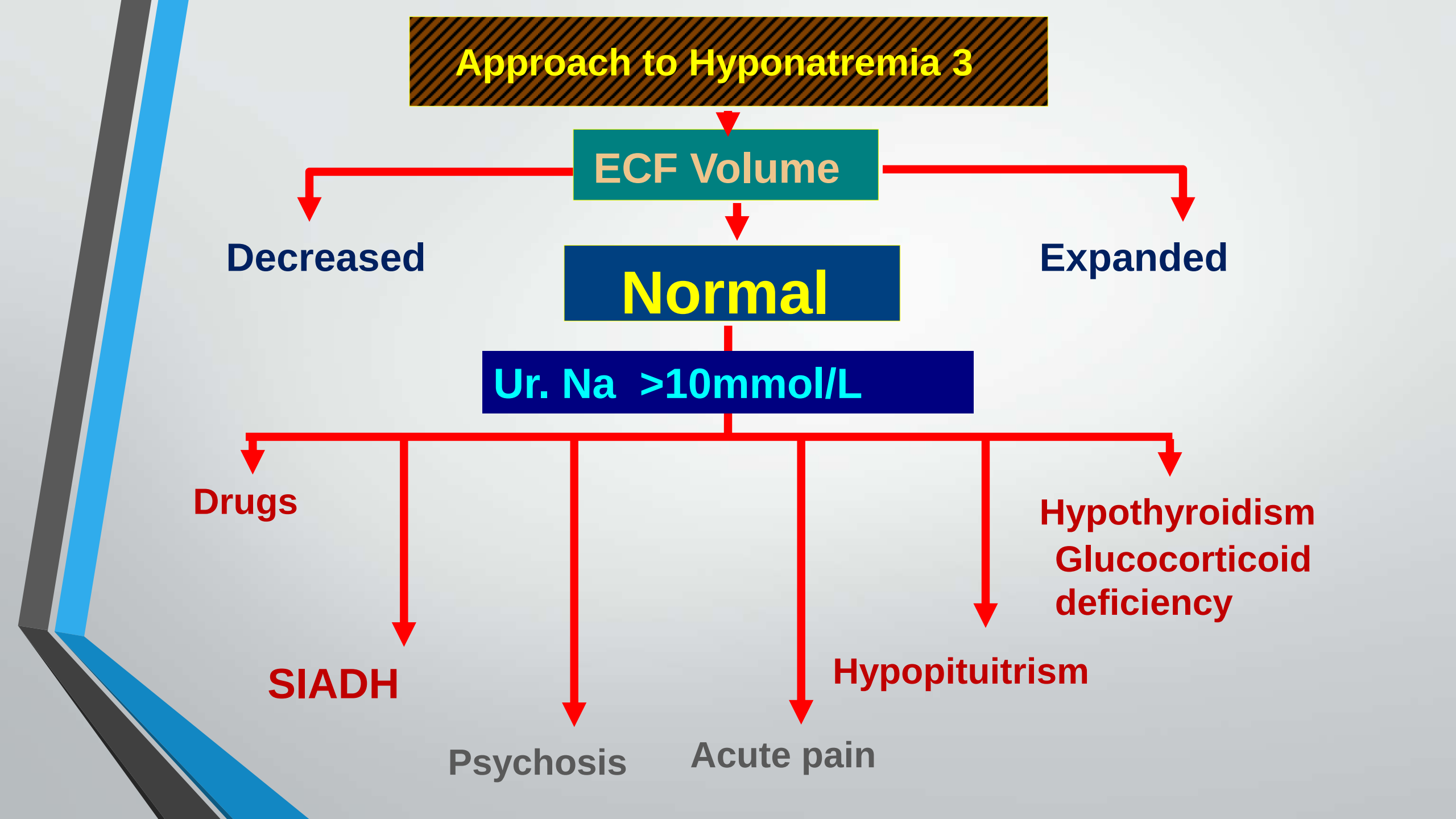

Approach to Hyponatremia
measure P. osmolality
Low
True Hyponatremia
Normal
Displacement
Psudohyponatremia
High
Osmotic
ECF Volume
Decreased
Normal
Expanded
Heart Failure
Liver cirrhosis
Nephrotic syndrome
Renal failure

Approach to Hyponatremia 2



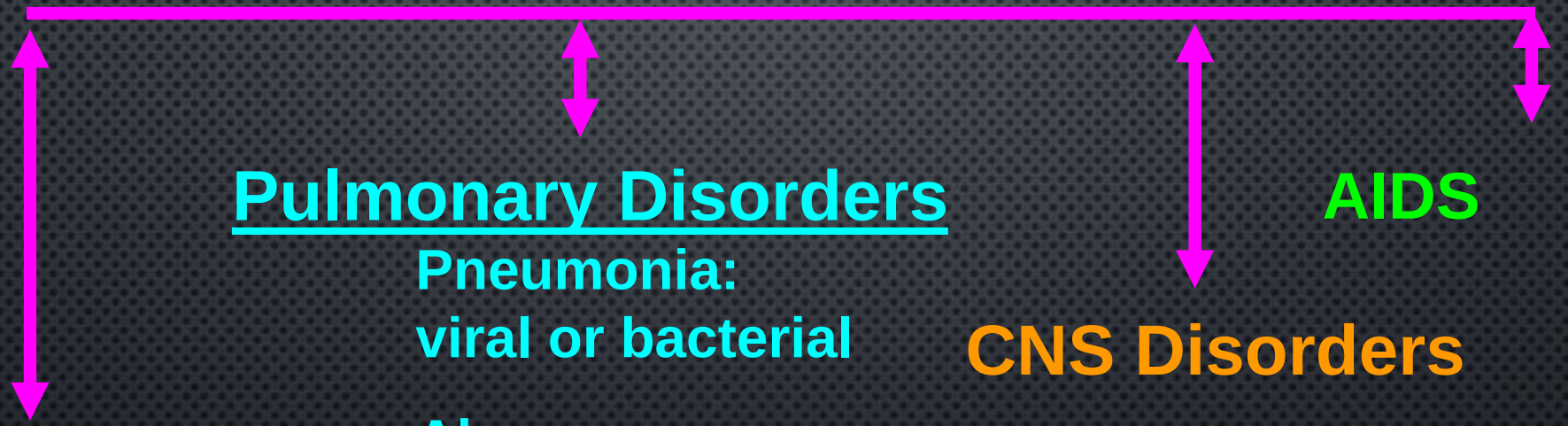
*Diarrhea *Vomiting
*Ileus *Cathartics
*Peritonitis *Pancreatitis
*Muscle damage *Burn

*Diuretics
*Osmotic diuretics
*Addison's disease
*Salt-loosing nephropathy


Approach to Hyponatremia 3
ECF Volume
Decreased
Normal
Expanded
Ur. Na >10mmol/L
Drugs
SIADH
Psychosis
Acute pain
Hypopituitrism
Hypothyroidism
Glucocorticoid deficiency

SIADH

Syndrome of Inappropriate Antidiuretic Hormone Secretion



Pulmonary Disorders

Pneumonia:
viral or bacterial

Abcess

TB

Aspergellosis

Carcinoma

Lung

Pancreas

Duodenum

AIDS

CNS Disorders

*Encephalitis *Meningitis
*Brain abscess *A. psychosis
*Head trauma *Stroke
*S.dural & s.arachnoid hrrge
*Guillian-Barre syndrome
*A. intermittent porphyria

NDT Advance Access published February 26, 2014

Clinical Practice Guideline

Clinical practice guideline on diagnosis and treatment of hyponatraemia

	SIADH	Cerebral salt wasting
Serum urea concentration	Normal–low	
Serum uric acid concentration	Low	
Urine volume	Normal–low	
Urine sodium concentration	>30 mmol/l	
Blood pressure	Normal	
Central venous pressure	Normal	

Case Scenario 1-5

- Diagnosis
  - Moderate / Severe Hyponatremia
  - Associated ECF expansion
  - Leading to cerebral manifestations
  - Impending Herniation??
  - + Hypokalemia - ?effect?
- **Management???**

Management of Hyponatremia

When to Treat:

* When there is s&s of hyponatremia
* Energetic treatment if ther is s&s of herniation

Herniation

Dilated fixed pupils, unilat. dil. pupils, CVS instability, hypoventillation, impaired temp. regulation

How to treat?????

Rate of Correction????

Case Scenario 1-6

- **Management**
  - **KCl 40 mEq/500 ml N. Saline infusion: ~80 ml/h**
  - **NaCl 3% ~45 ml/h**

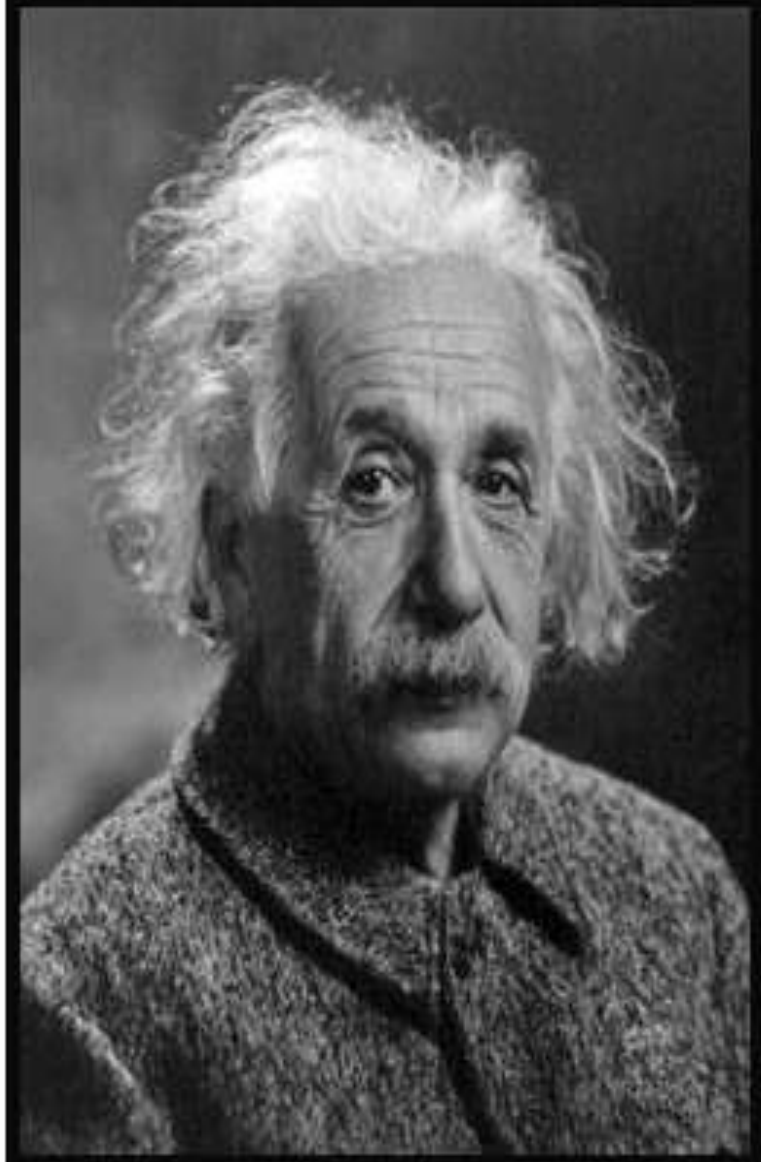
- 4-6 hrs later patient improves: communicative and moves her limbs – SNa 110, SK 3.4
- Another 8 hrs later: patient ……..

Case Scenario 1-7

- Management
  - KCl 40 mEq/500 ml N. Saline infusion: ~80 ml/h
  - NaCl 3% 45 ml/h

- Another 8 hrs later she deteriorates with dysarthria, quadriparesis & seizures – SNa 128, K 4.0


try
and
fail
don't
fail
to
try

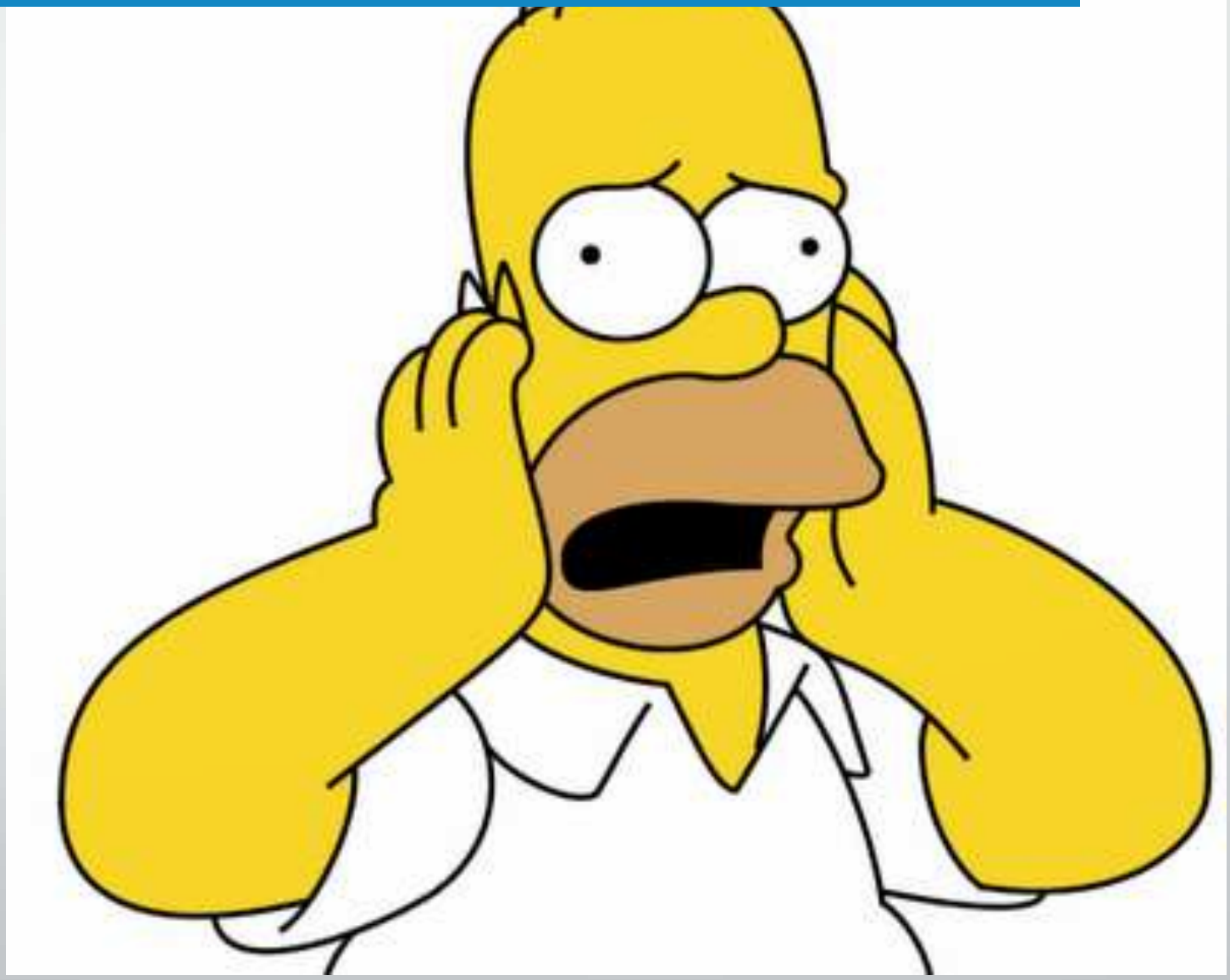


We can't solve problems by using the same kind of thinking we used when we created them.

(Albert Einstein)

Case Scenario 1-8

- MRI Brain



Case Scenario 1-9

- **MRI Brain:**
  - Axial T2-weighted image
  - shows edema in central pons (arrows) and preservation of tegmentum & ventrolateral aspects of pons.

Management of Hyponatremia

When to Treat:

* When there is s&s of hyponatremia
* Energetic treatment if ther is s&s of herniation

Herniation

Dilated fixed pupils, unilat. dil. pupils, CVS instability, hypoventillation, impaired temp. regulation

Rate of Correction:

Not > 10 mmol/L 1st day then < 8 mmol/L/day to <130 mmol/L to avoid:

Osmotic Demy-elination Synd.

Fluct. conscious., dysarthria, dysphonia, para- & quadripresis, seizures & coma

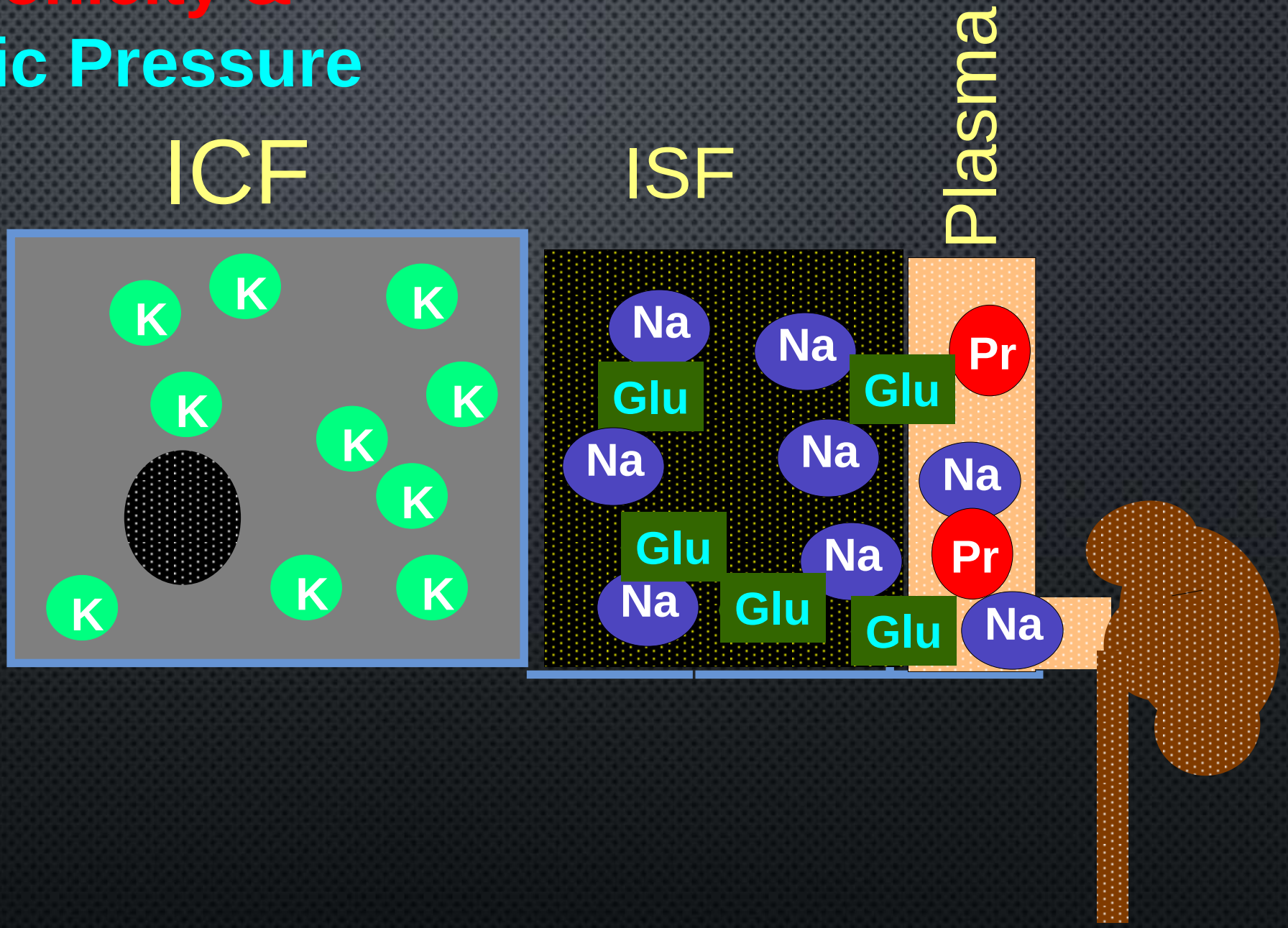
"Damned if we do, damned if we don't"

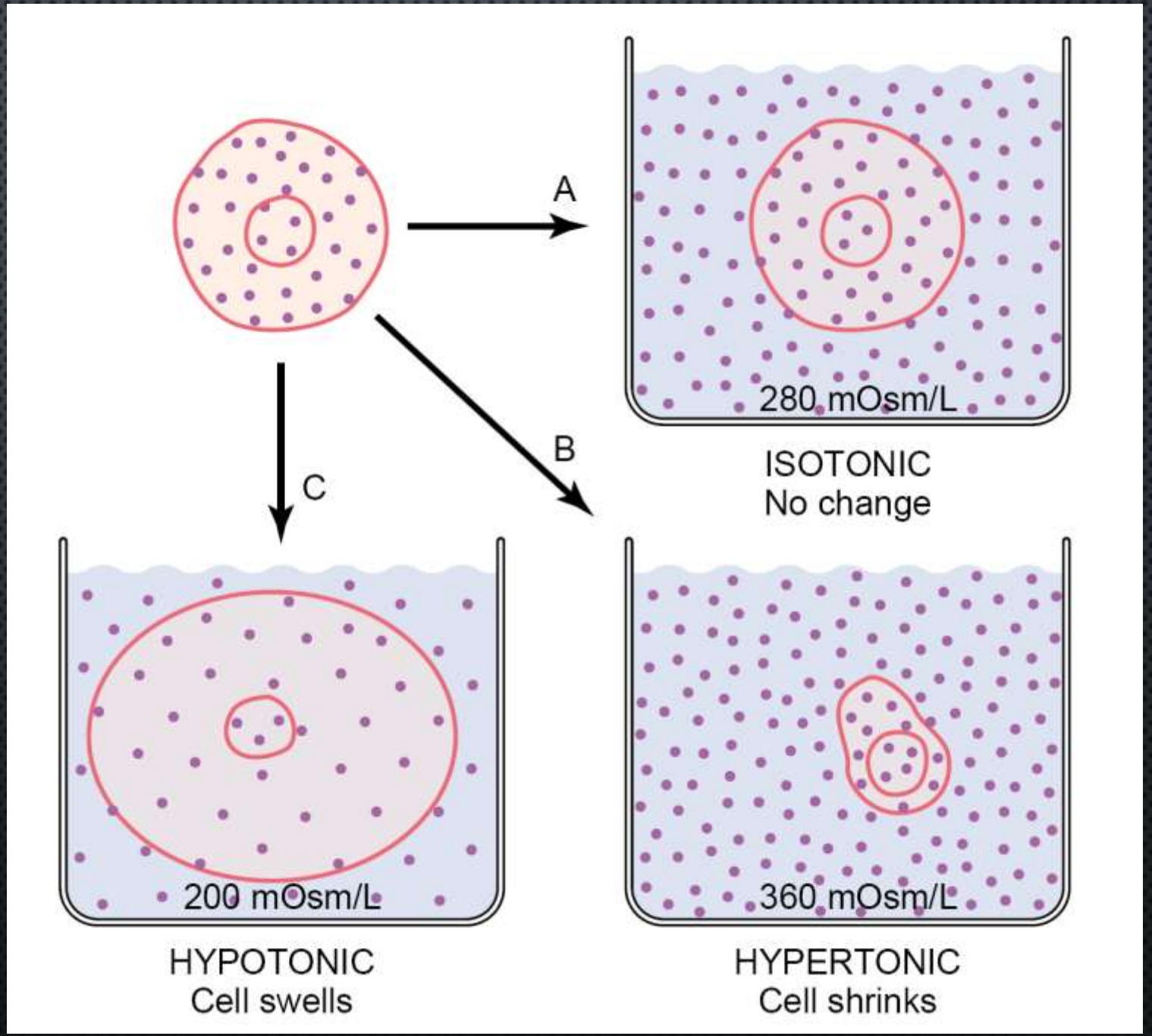
Oh MS, Kim Hi, Carrol HJ.

Recommendations for treatment of symptomatic hyponatremia.

Nephron 1995;70:143-50

Extracellular Tonicity &
Plasma Oncotic Pressure




A
B
C
280 mOsm/L
ISOTONIC
No change
200 mOsm/L
HYPOTONIC
Cell swells
360 mOsm/L
HYPERTONIC
Cell shrinks

AMA Arch Neurol Psychiat **1959**; 81:154–172

Central pontine myelinolysis:

a hitherto undescribed disease occurring in alcoholic and malnourished patients.

Adams RD, Victor M, Mancall EL

A series of 4 patients

quadriparesis, pseudobulbar paralysis

characteristic pattern of myelin loss confined within central pons.

No evidence of inflammation

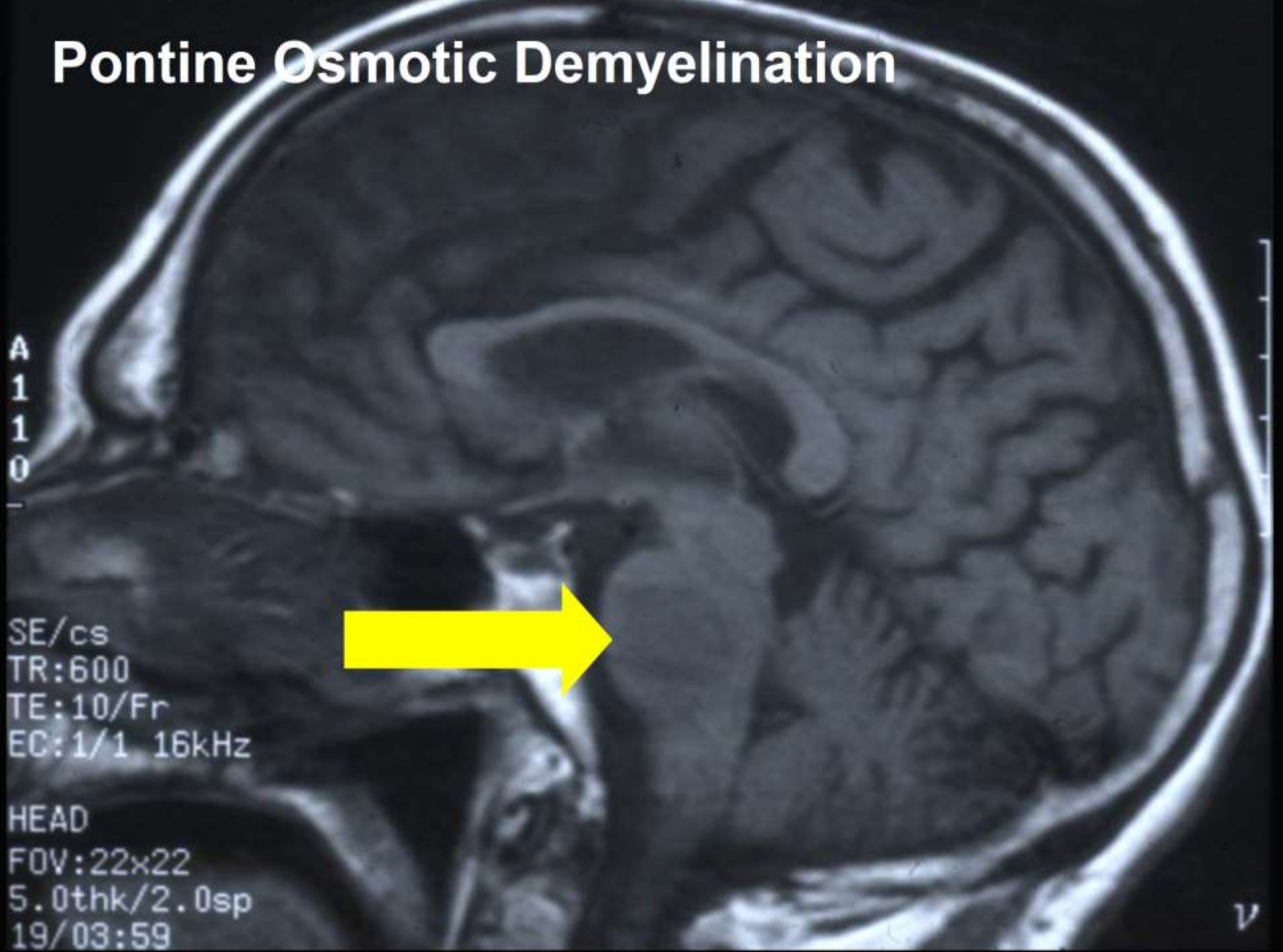
(differentiating from known demyelinating disease like multiple sclerosis)

3 patients were alcoholics, malnourished and chronically ill

Authors called it "new disease" and termed it

CENTRAL PONTINE **MYELINOLYSIS**

Pontine Osmotic Demyelination



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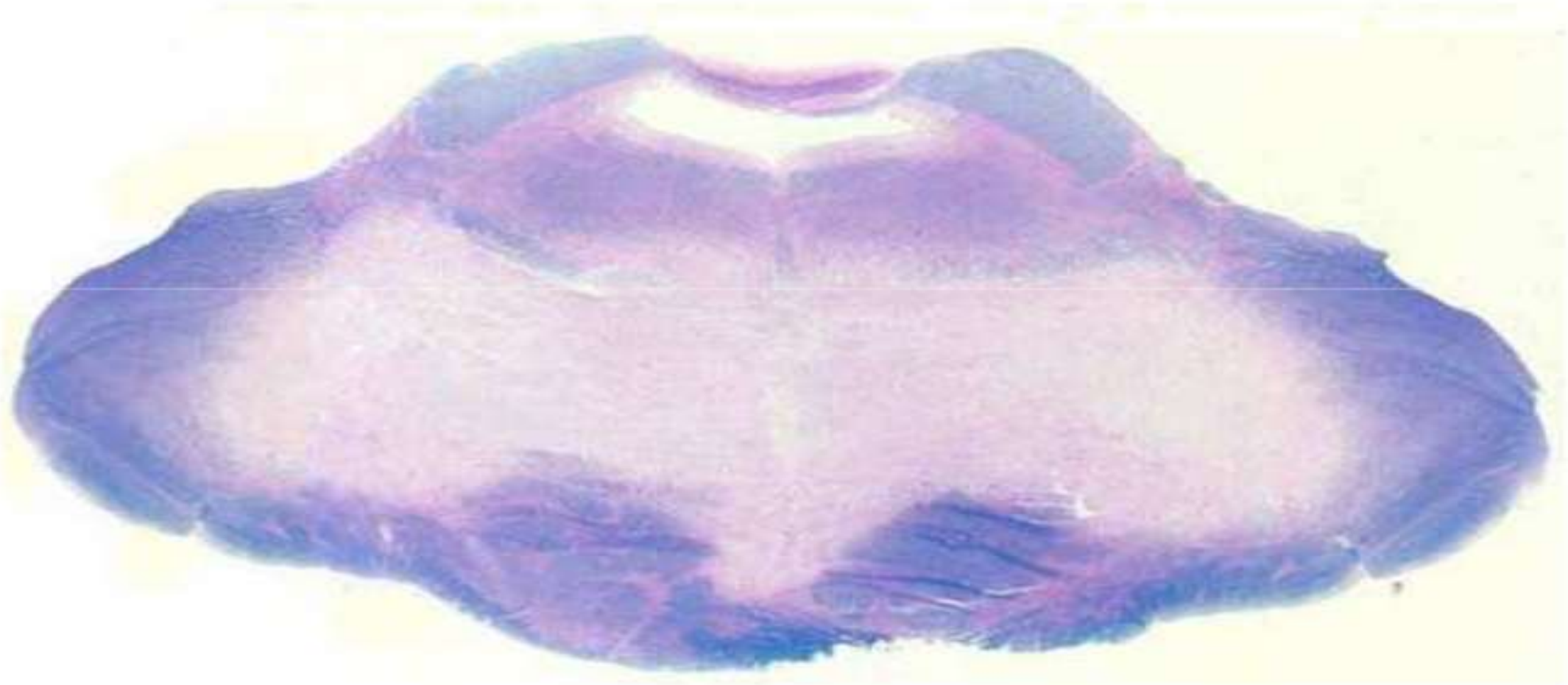


Classic histopathology of the pons in CPM showing a symmetrical, central bat-wing area of demyelination affecting most of the pontine base. Luxol-fast blue/PAS

1966

More lesions identified and not localized to the Pons

basal ganglia,
thalamus,
Gray-white junction of cerebral and cerebellar cortices,
lateral geniculate

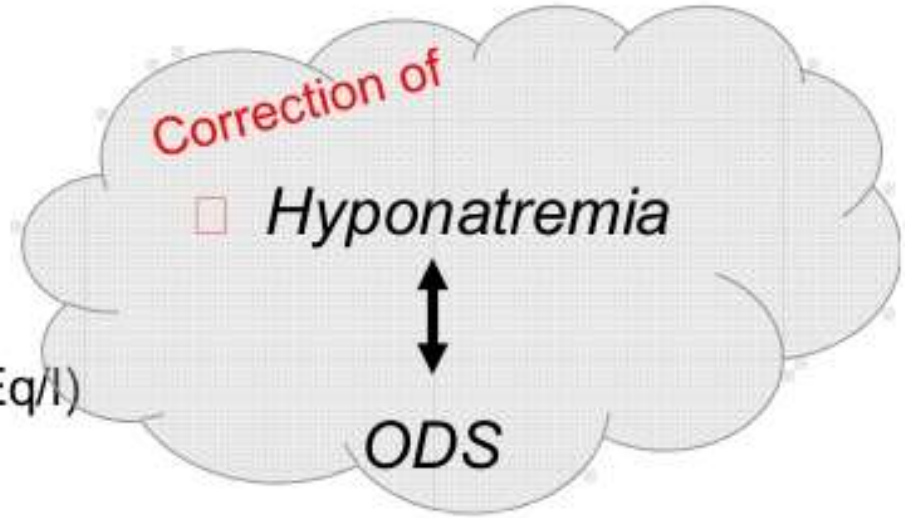
Most of the cases occurred in chronic conditions such as liver disease, sepsis, burns, and cancer
ie
It occurred in presence of co-existing diseases/ conditions

Tomlinson BE, Pierides AM, Bradley WG
Central pontine myelinolysis. Two cases with associated electrolyte disturbance
QJM. **1976**;45:373-86.

2 cases

protracted vomiting and drowsiness

severe hyponatraemia (serum sodium 96–100 mEq/l)



Correction of electrolyte abnormalities was accompanied by deterioration in the level of consciousness, quadriparesis, dysphasia and mutism

Postmortem examination
finding of CPM and EPM

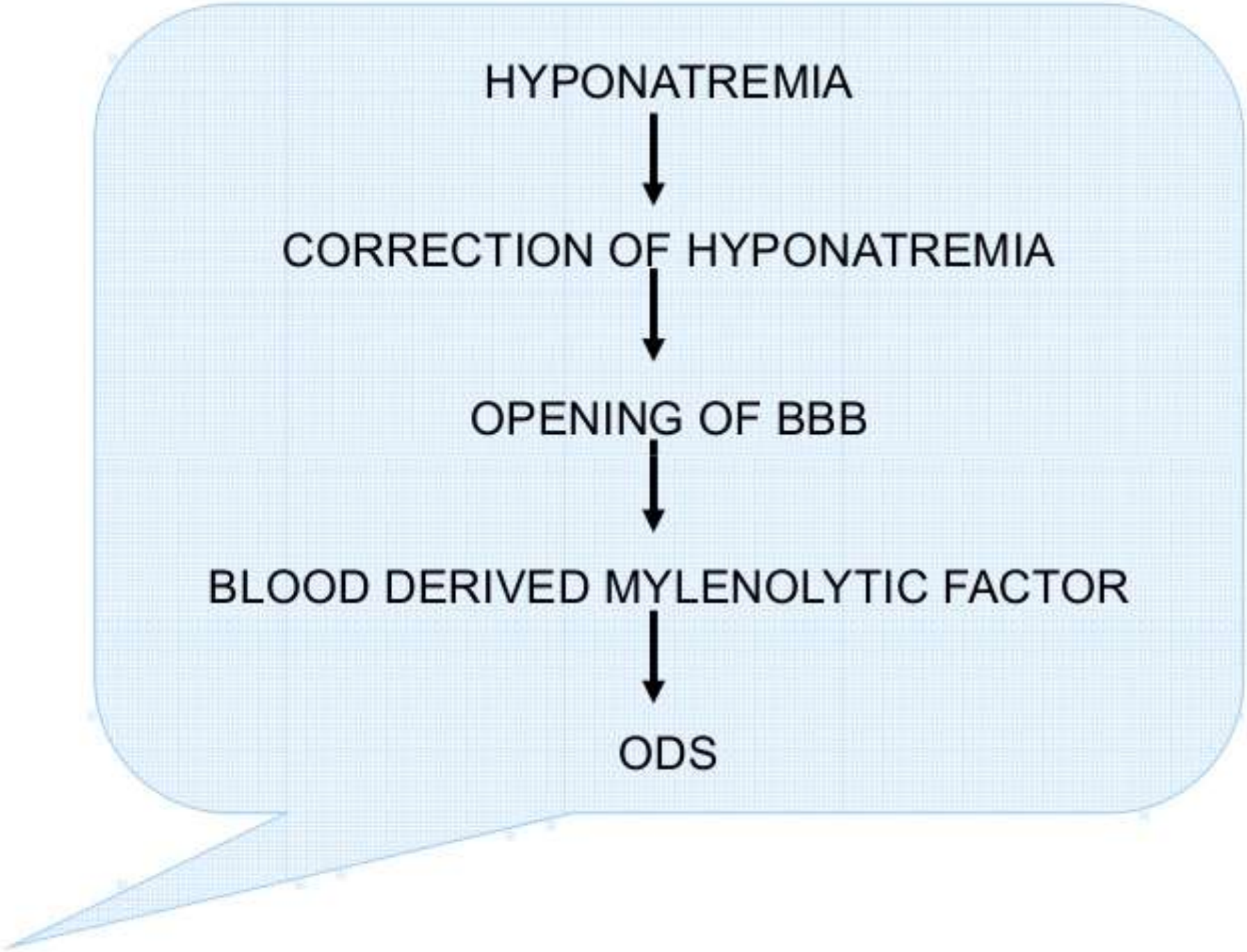
1979: Kevin Leslie
Pathology resident at the University of Colorado

Autopsy of a Jaundiced patient with CPM

breakdown of BBB
Exit of albumin-bound bile pigment from blood stream into brain tissues.

Blood derived MYELINOLYTIC factor
Complements, immunoglobulins

Several reports of
similar green discoloration of the pons
in patients with CPM who had concurrent liver disease and jaundice


HYPONATREMIA
CORRECTION OF HYPONATREMIA
OPENING OF BBB
BLOOD DERIVED MYLENOLYTIC FACTOR
ODS

Brightman 1973, Rapoport 1976

BBB could be opened by intravenous Hypertonic saline

Endothelial cell dehydration and shrinkage
impairment of endothelial tight junctions

Neurosurgeons were using this strategy
to deliver chemotherapeutic drugs
that were impermeable to BBB

Why specific areas of brain affected

Gray matter is 10 times rich in capillaries than white matter

If some myelnotoxic factor is responsible for demyelination

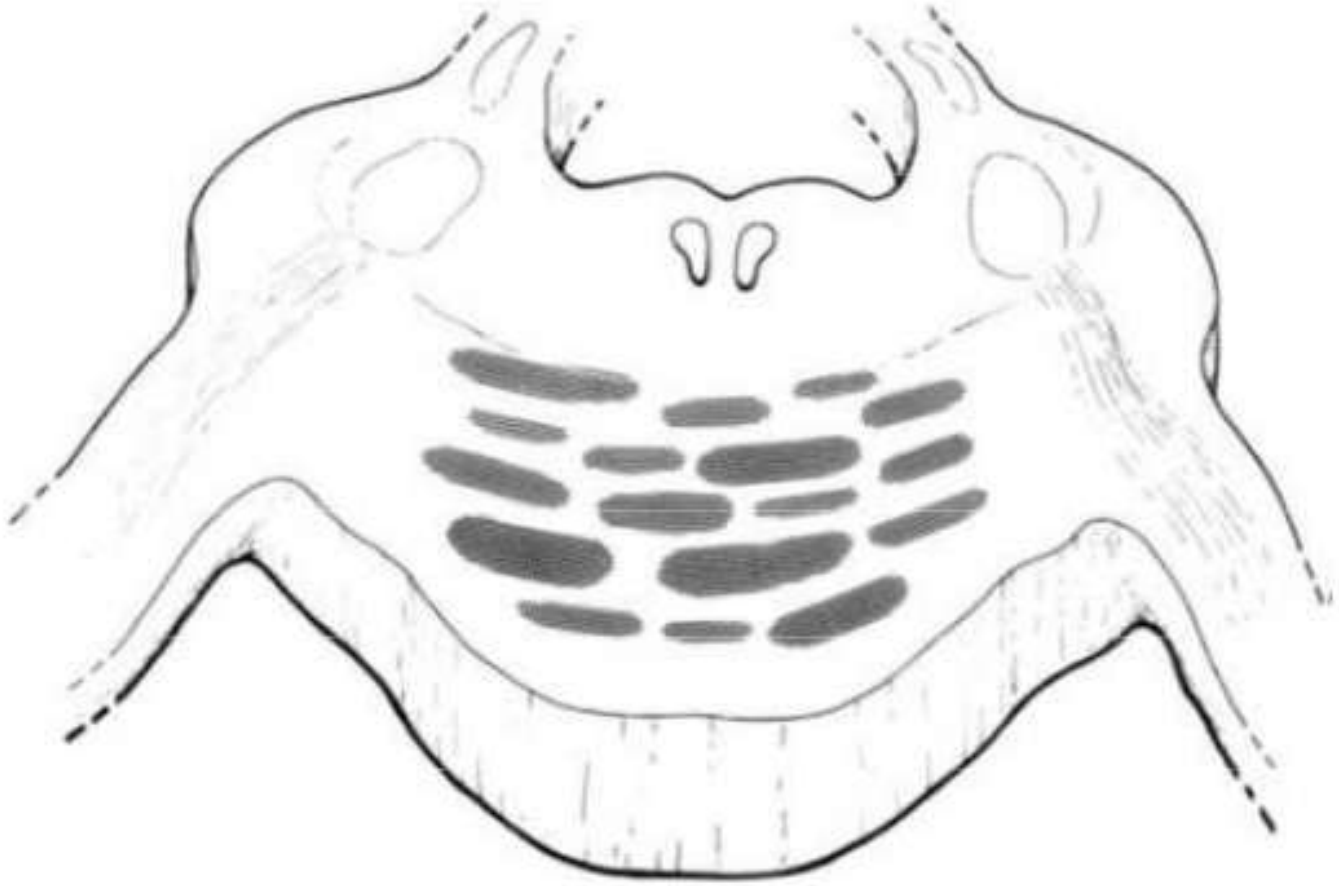
This factor would be enriched in GRAY matter

while substrate MYELIN would be present in immediately adjacent WHITE matter

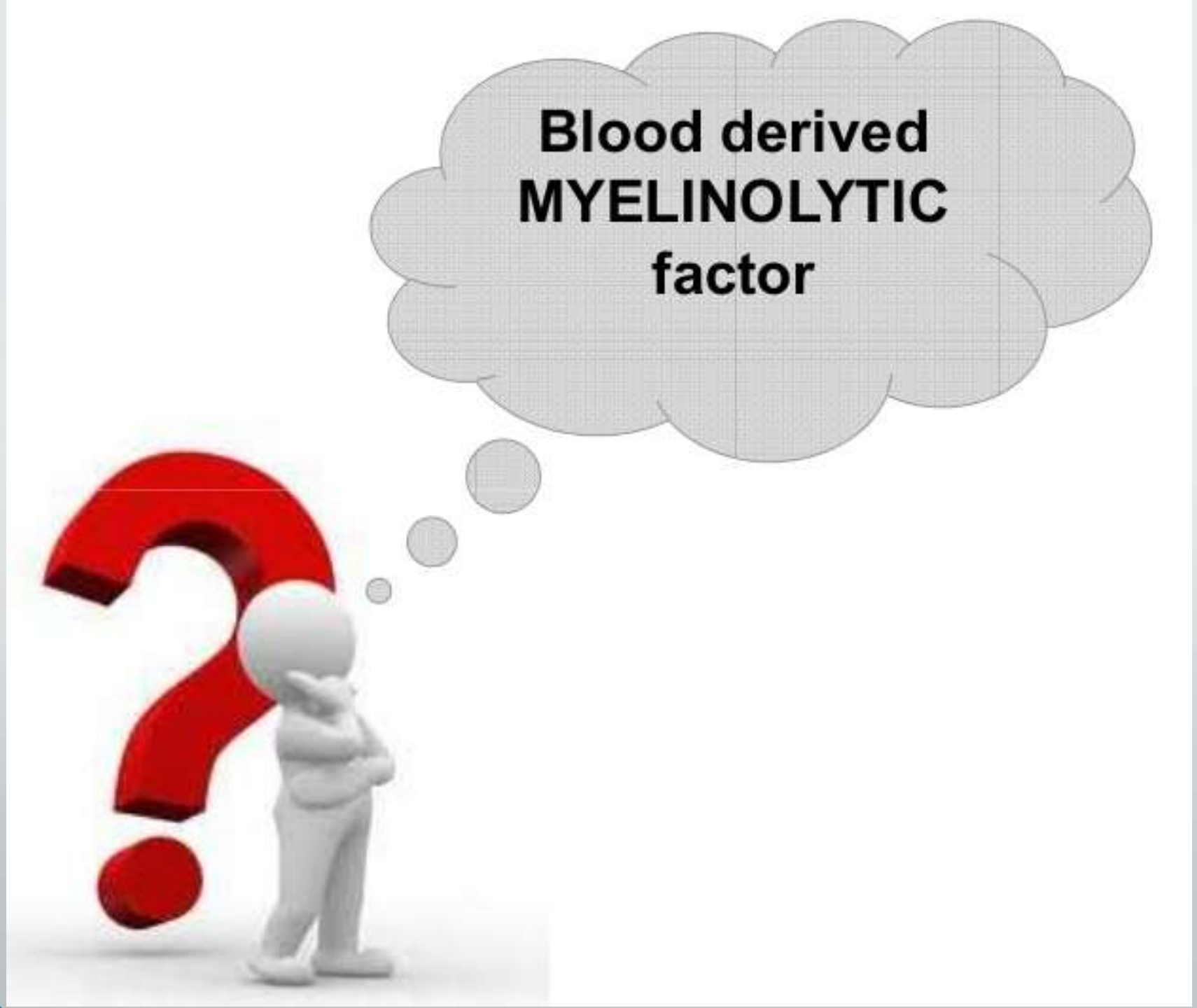
Areas with rich admixture of GRAY and WHITE matter would be at greatest risk

These areas are
PONS, thalamus, striatum

Why specific areas of brain affected



Sketch of Human Pons
close admixture of white matter bundles within gray matter


Blood derived
MYELINOLYTIC
factor

1982: Norenberg

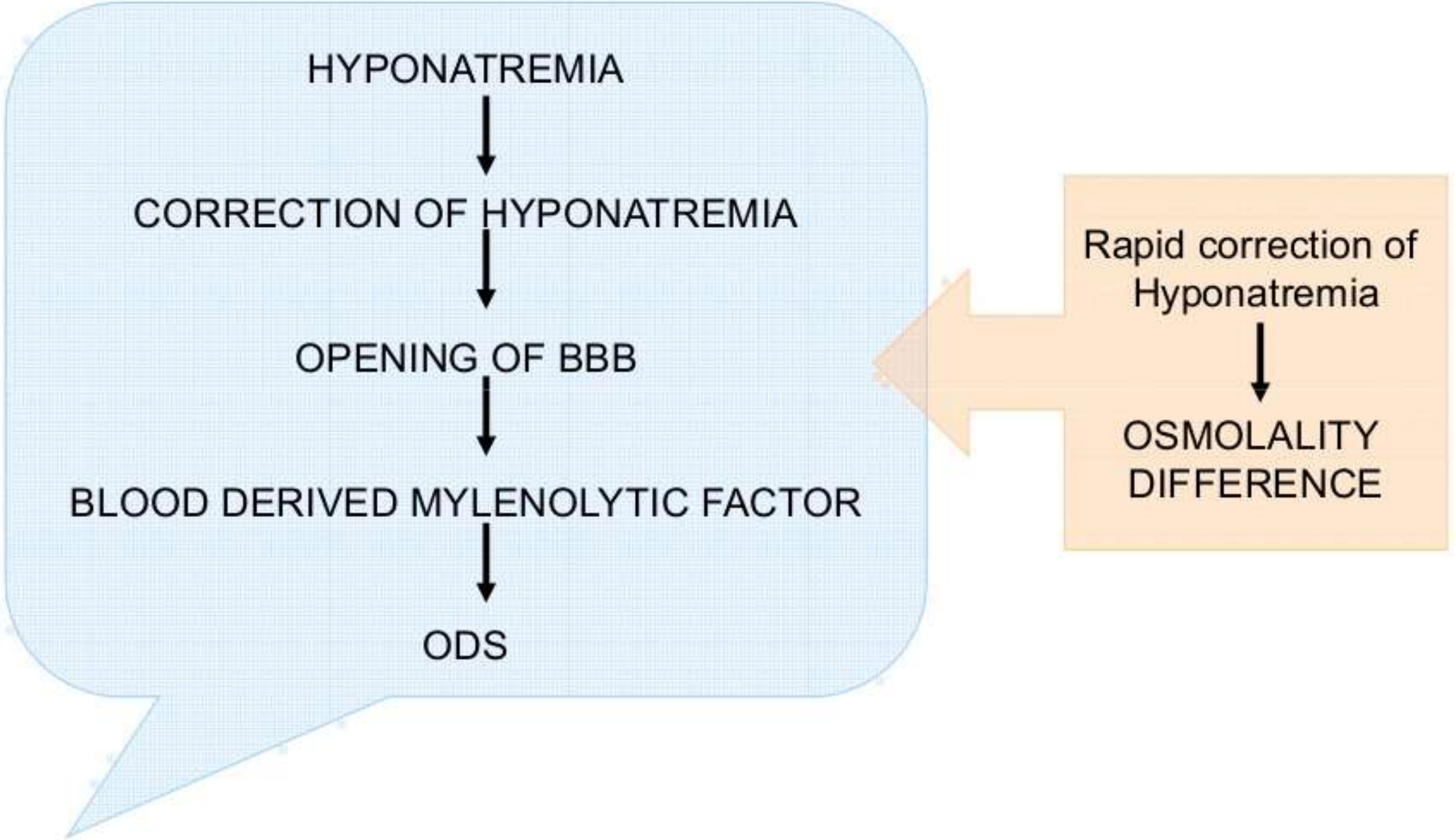
Case report

Normonatremic (S.Na-139) patient with hepatic encephalopathy
Treated with lactulose

On Day10,
S.Na increased to 171 meq/L

Patient became restless and confused and died on D20

Histopathology showed demyelinating lesion in centre of pontine base


HYPONATREMIA
CORRECTION OF HYPONATREMIA
OPENING OF BBB
BLOOD DERIVED MYLENOLYTIC FACTOR
ODS
Rapid correction of Hyponatremia
OSMOLALITY DIFFERENCE

1984:NORENBERG

Rapid correction of hyponatremia in

Patient with short duration hyponatremia (hours to few days),
did not develop CPM.

But those with longer duration (1 week or longer),
developed CPM.

Michael D. Norenberg, Rebecca E. Papendick
Chronicity of hyponatremia as a factor in experimental myelinolysis
Annals of Neurology 1984;15(6): 544–547

Rats hyponatremic for 1 day compared with another group hyponatremic for 3 days

3-day hyponatremic rats
developed more numerous and more severe demyelinative lesions
than the 1-day rats

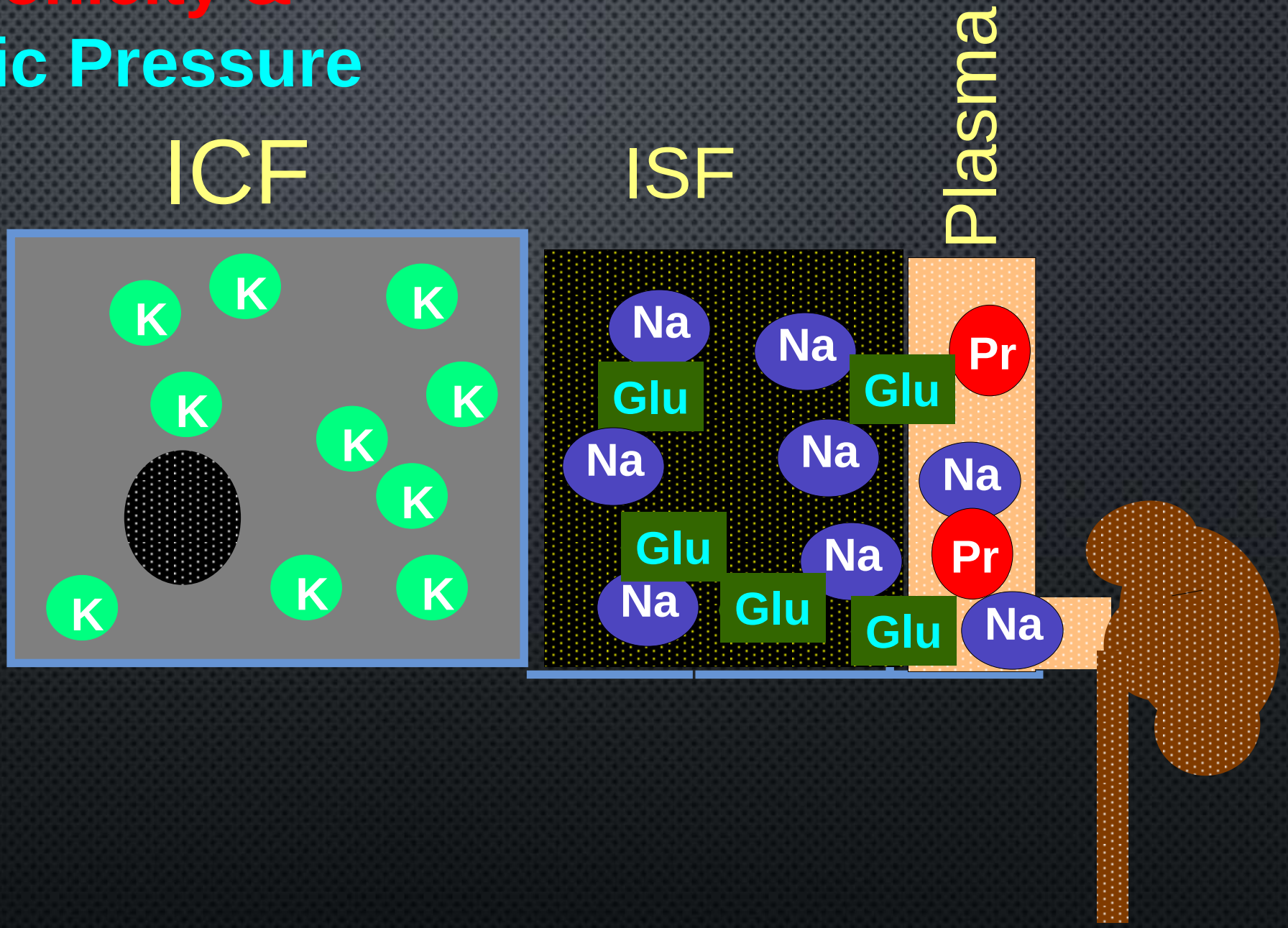
Rapid change in Osmolality **without** change in S.Na has been reported to led to ODS

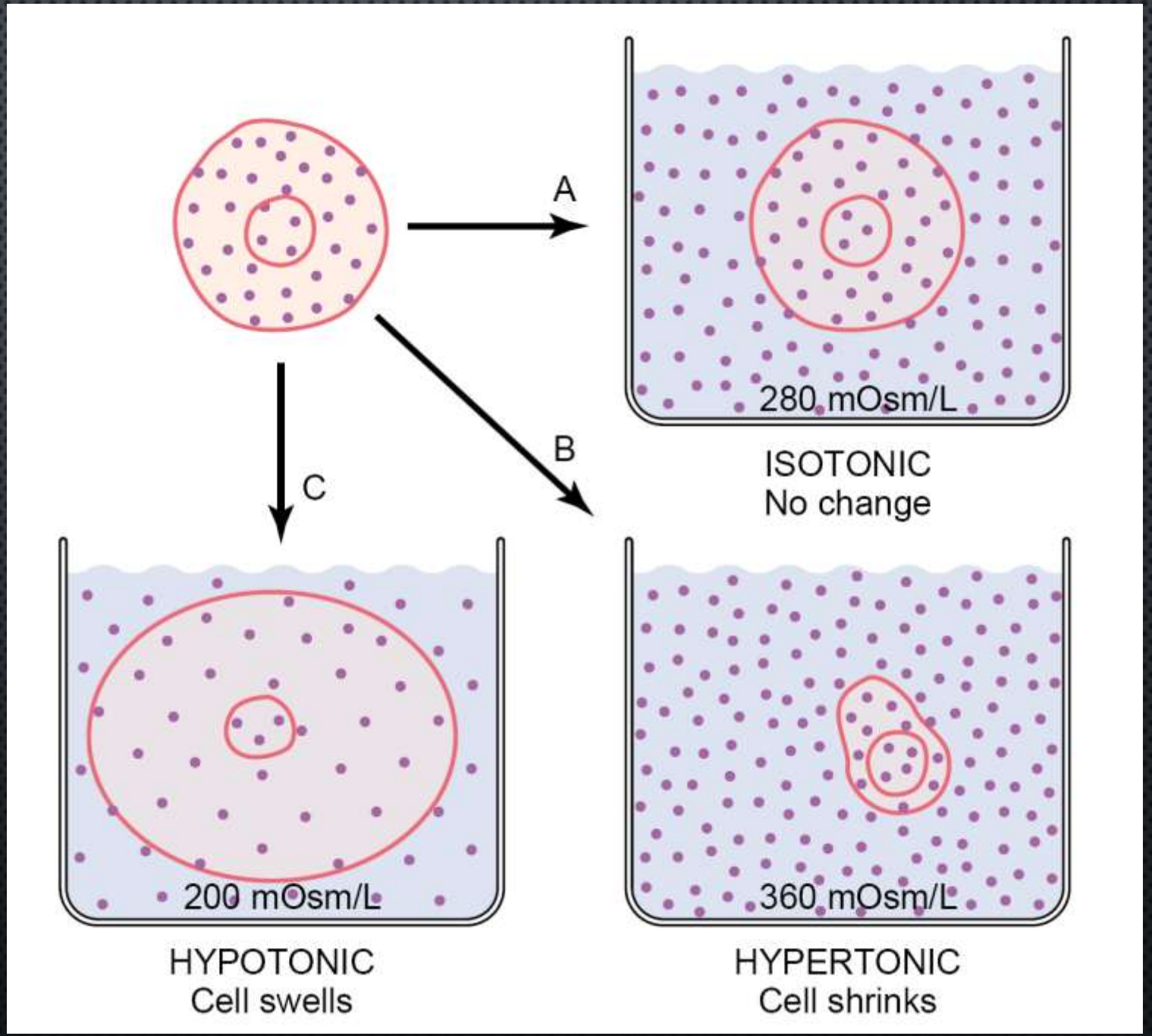
- In Post liver transplant patients
- Dialysis disequilibrium syndrome
- Treatment of hyperammonemic patients

- Correction of hypernatremia and hyperglycemia

REAL CULPRIT
OSMOLALITY CHANGE

Extracellular Tonicity &
Plasma Oncotic Pressure




A
B
C
280 mOsm/L
ISOTONIC
No change
200 mOsm/L
HYPOTONIC
Cell swells
360 mOsm/L
HYPERTONIC
Cell shrinks

Effect of co existing other electrolyte and metabolic disturbances

increased risk of ODS

HYPOKALEMIA

Concomitant hypokalemia potentiates osmolality difference between intracellular and extracellular compartment

Na is corrected more rapidly, when hypokalemia is corrected along with hyponatremia
Increased activity of NaKATPase

Hypophosphatemia

Pi is required for synthesis of two organic osmolytes, phosphocreatine and glycerolphosphorylcholine

Effect of co existing other electrolyte and metabolic disturbances

UREMIA

Protective effect

In azotemic rats, Brain myoinositol (organic osmolyte) levels increased more quickly during rapid correction of hyponatremia

DISEASES ASSOCIATED WITH ODS

Alcoholism

Malnutrition

Post liver transplant

Prolonged diuretic use

Psychogenic polydypsia

Burns

Post pituitary surgery

Post surgery: urological, gynecological

LIVER DISEASE AND ORTHOTROPIC LIVER TRANSPLANTATION

Often associated **hyponatremia**

Malnourished

decreased intracellular myo ionositol level

Reduced myo ionositol level has been documented in these patients

Cultured astrocytes treated with ammonia show reduced myo ionositol levels.

Ammonia impairs uptake of myo ionositol by astrocytes.

Other organic osmolytes (taurine, glycerophosphorylcholine) are reduced in patients with hepatic encephalopathy

IMAGING

MRI:imaging of choice

Hyperintense lesion on T2 weighted
Hypointense lesion on T1 weighted
DWI might have capability of detecting lesion undetectable on T2

TIMING

Timing of appearance may be delayed

MR image typically are normal at the onset of symptoms and become positive after approximately 2 weeks

If diagnosis remains likely: repeat imaging at 10-14 days may reveal lesion

LESIONS OF ODS

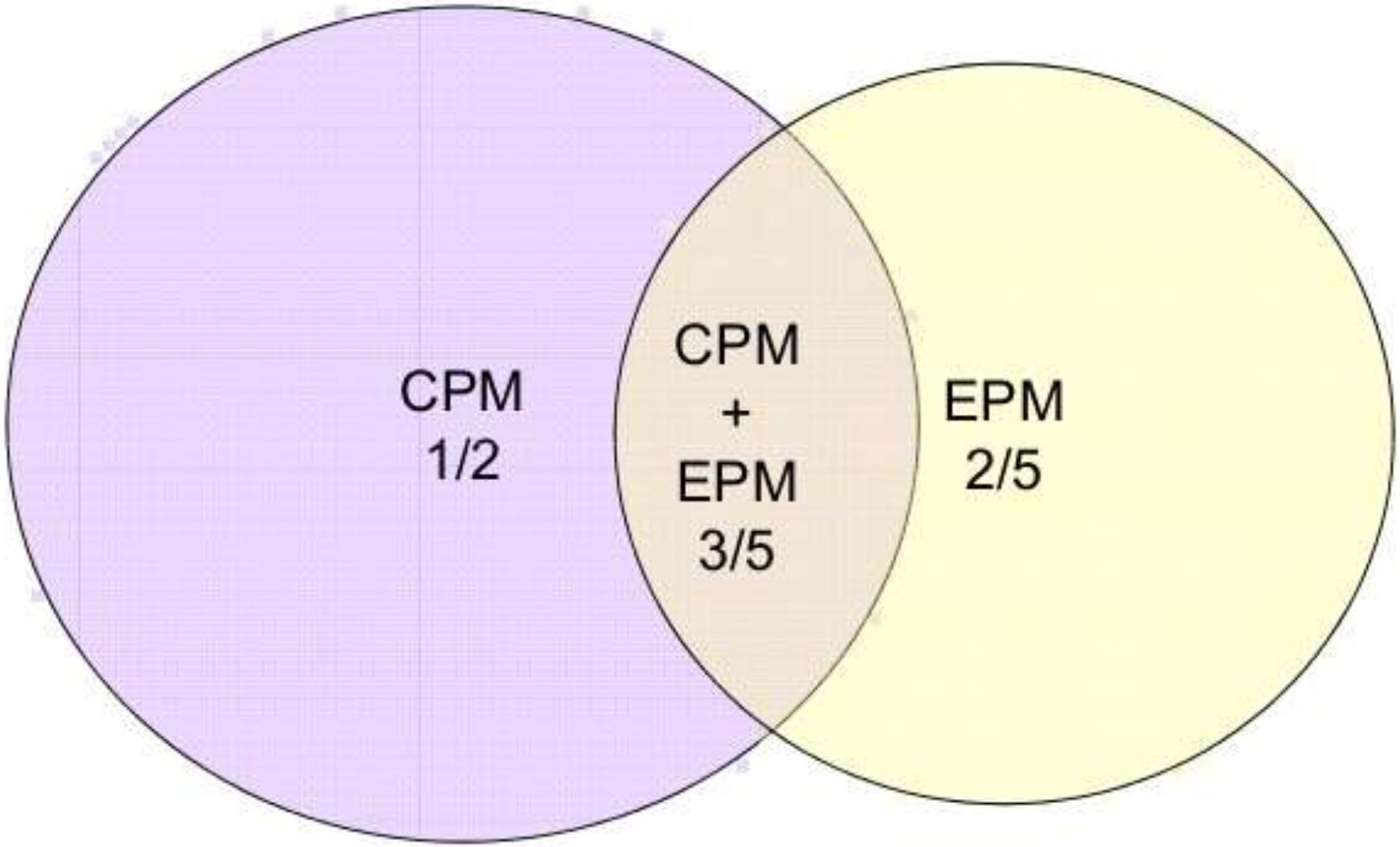
Pons
Cerebellum
Lateral geniculate body
External capsule
Hippocampus
Putamen
Cerebral cortex/ subcortex
Thalamus
Caudate nucleus

Claustrum
Internal capsule
Midbrain
Internal medullary lamella
Mamillary body
Medulla oblongata

MICROSCOPY

Degeneration and loss of
oligodendrocytes
with preservation of axons unless lesion is advanced

RELATIVE PROPORTIONS OF CPM AND EPM



TREATMENT

Prevention
Judicious correction of Hyponatremia

Selective vasopressin receptor antagonis
For euvolumic or hypervolumic hyponatremia

Corticosteroids
Used to mitigate severity of ODS
? Stabilization of BBB
Timing of administration not well determined

Myoinositol
Improve mortality in rats with rapid correction of hyponatremia

Plasmapheresis
Appeared beneficial in series of 4 patients with ODS
? Reduction in inflammatory mediators and preservation of BBB

TREATMENT

Re induction of Hyponatremia

in chronic hyponatremic rats who had roughly
30 meq/L change in S.serum Na in 12 hours

Reinduction of mild hyponatremia reduced
both neurological manifestation and mortlaity from 100% to 6%

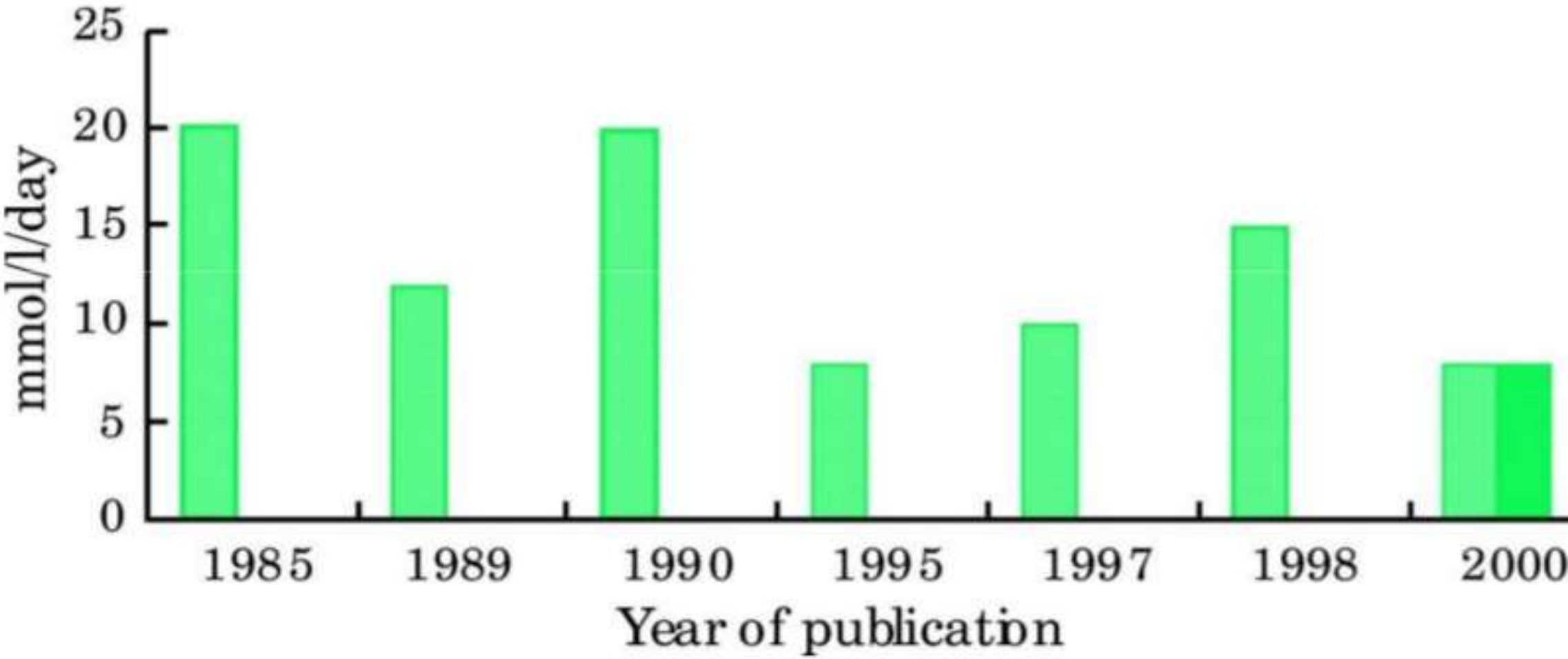
Kidney Int. 2009 Sep;76(6):614-21
Re-induction of hyponatremia after rapid overcorrection of hyponatremia reduces mortality in rats.
Gankam Kengne F, Soupart A, Pochet R, Brion JP, Decaux G

Case reports showing improvement in neurological symptoms
after re induction of hyponatremia

Oya S, Tsutsumi K, Ueki K, et al.
Reinduction of hyponatremia to treat central pontine myelinolysis.
Neurology 2001;57:1931–2

Soupart A, Ngassa M, Decaux G.
Therapeutic relowering of the serum sodium in a patient after excessive correction of hyponatremia.
Clin Nephrol 1999;51:383– 6

SUGGESTED MAXIMUM CORRECTION OF HYPONATREMIA



Rate of correction

Symptomatic
or
Acute hyponatremia
(change >0.5 meq/L/h or onset in < 48 hours)

→ 1-2 meq/L/h (10-12 meq/L/day)

Chronic hyponatremia
(Change over > 48 hours or unknown duration)
Increased risk of CPM
as adaptive mechanism has occured

→ 0.5 meq/L/h (8-10 meq/L/day)

GOAL of Correction

120-130 meq/L
Lower in patients with s.Na<105

Case Scenario 1-10

- **Management of the case after ODS:**
  - Stop conc Saline
  - Give dextrose 5% in water; 1% of body weight over 8 hours with monitoring sNa, K.
  - Repeat until SNa Decreases to previous level 114
  - Neurological follow up
- The patient improves gradually over several days
- In 3 weeks she returns to pre-illness state

Clinical practice guideline on diagnosis and treatment of hyponatraemia

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7.1.1. First-hour management, regardless of whether hyponatraemia is acute or chronic

7.1.1.1. We recommend prompt i.v. infusion of 150 ml 3% hypertonic over 20 min (1D).

7.1.1.2. We suggest checking the serum sodium concentration after 20 min while repeating an infusion of 150 ml 3% hypertonic saline for the next 20 min (2D).

7.1.1.3. We suggest repeating therapeutic recommendations 7.1.1.1 and 7.1.1.2 twice or until a target of 5 mmol/l increase in serum sodium concentration is achieved (2D).

7.1.1.4. Manage patients with severely symptomatic hyponatraemia in an environment where close biochemical and clinical monitoring can be provided (not graded).

$$\text{Change in serum } (Na^+) = \frac{\text{infusate } (Na^+) + \text{infusate } (K^+) - \text{serum } (Na^+)}{\text{total body water} + 1}$$

7.2. Hyponatraemia with moderately severe symptoms

7.2.1.1. We recommend starting prompt diagnostic assessment (1D).

7.2.1.2. Stop, if possible, medications and other factors that can contribute to or provoke hyponatraemia (not graded).

7.2.1.3. We recommend cause-specific treatment (1D).

7.2.1.4. We suggest immediate treatment with a single i.v. infusion of 150 ml 3% hypertonic saline or equivalent over 20 min (2D).

7.2.1.5. We suggest aiming for a 5 mmol/l per 24-h increase in serum sodium concentration (2D).

7.2.1.6. We suggest limiting the increase in serum sodium concentration to 10 mmol/l in the first 24 h and 8 mmol/l during every 24 h thereafter, until a serum sodium concentration of 130 mmol/l is reached (2D).

7.2.1.7. We suggest checking the serum sodium concentration after 1, 6 and 12 h (2D).

7.2.1.8. We suggest additional diagnostic exploration for other causes of the symptoms if the symptoms do not improve with an increase in serum sodium concentration (2D).

7.2.1.9. We suggest considering to manage the patient as in severely symptomatic hyponatraemia if the serum sodium concentration further decreases despite treating the underlying diagnosis (2D).

7.5. What to do if hyponatraemia is corrected too rapidly?

7.5.1.1. We recommend prompt intervention for re-lowering the serum sodium concentration if it increases >10 mmol/l during the first 24 h or >8 mmol/l in any 24 h thereafter (1D).

7.5.1.2. We recommend discontinuing the ongoing active treatment (1D).

7.5.1.3. We recommend consulting an expert to discuss if it is appropriate to start an infusion of 10 ml/kg body weight of electrolyte-free water (e.g. glucose solutions) over 1 h under strict monitoring of urine output and fluid balance (1D).

7.5.1.4. We recommend consulting an expert to discuss if it is appropriate to add i.v. desmopressin 2 μg, with the understanding that this should not be repeated more frequently than every 8 h (1D).

Osmotic Demyelination Syndrome in End-Stage Renal Disease After Recent Hemodialysis: MRI of the Brain

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OBJECTIVE. Osmotic demyelination syndrome has been reported in patients with end-stage renal disease, but the specific MRI findings in this patient group have not been documented in detail. Our aims were to present the brain MRI findings during an episode after hemodialysis and at follow-up, and to identify possible factors that may contribute to lesion development.

MATERIALS AND METHODS. Seventeen patients with osmotic demyelination syndrome who had undergone hemodialysis at least once and had brain MRI examinations were retrospectively reviewed. Neurologic and MRI examinations were performed during a clinical episode. Serum levels of sodium, creatinine, blood urea nitrogen, and glucose were assessed, and serum osmolality and the ratio of blood urea nitrogen to creatinine (BUN:Cr) were calculated. Follow-up MRI was performed in nine cases. Laboratory and imaging findings were evaluated.

RESULTS. An altered level of consciousness and convulsions were the most common neurologic symptoms. The pons was involved in 11 patients (65%) and extrapontine sites in 12 (71%). Four patients had dysequilibrium syndrome. Follow-up MRI showed complete resolution in six patients and lesion reduction in three within a short time. The most common biochemical changes at the time of MRI were hyponatremia and low BUN:Cr in the blood.

AJR 2004;182:809–816

Thank You

NAGY SAYED-AHMED